REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the following remarks.

Status of the Claims

Claims 1-4, 10 and 11 are currently pending in the present application. The Office Action is non-final. Claim 11 has been withdrawn from further consideration as being drawn to a non-elected invention. Since no new amendments were made to the claims, no new matter was added.

Based upon the above considerations, entry of the present Response is respectfully requested.

Claim for Foreign Priority

Within the Office Action dated February 2, 2009 (hereinafter "Office Action"), the Examiner indicated in item 12 of the Office Action Summary page that the Examiner acknowledges the claim for foreign priority. However, the Examiner indicates that no certified copy of the priority document has been received. Applicants note that Form PCT/IB/304 was filed on September 21, 2006, which indicates that certified priority documents were received by WIPO. Applicants respectfully request that the Examiner recheck the application file for certified copies of the foreign priority documents.

Issues Under 35 U.S.C. § 103(a), Obviousness

Claims 1-4 and 10 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Leclef *et al.*, U.S. Patent No. 5,100,591 (hereinafter "Leclef"), in view of Chen *et al.*, U.S. Patent No. 6,537,813 (hereinafter "Chen"). Applicants respectfully traverse this rejection.

The Examiner asserts that Leclef describes a process for preparing lipid microparticles possessing an affinity for phospholipids, wherein the water-insoluble microparticles and the phospholipid are dissolved in a common organic solvent, and the solution is subsequently mixed with an aqueous solution in an amount such that an insolubilization takes place in the form of a precipitate, and the organic solution is removed to recover an aqueous solution containing the microparticles in the form of a microsuspension. The Examiner states that Leclef does not describe mixing the two solutions via a device equipped with a mixing means, however, the Examiner asserts that such was known in the prior art. The Examiner further asserts that Chen describes concurrent flow mixing methods and apparatuses for the preparation of gene therapeutic compositions, relating to making mixtures and condensate compositions via controlled and uniform mixing of various compositions (*See* pages 3-4 of the Office Action). Applicants respectfully disagree.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level

of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (*e.g.*, commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. But before the Examiner can utilize these guidelines, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*; *supra*. To reject a claim based on the above mentioned guidelines, the Examiner must resolve the *Graham* factual inquiries. MPEP § 2143.

If the Examiner resolves the *Graham* factual inquiries, then the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 sets forth the rationales that were established in *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Applicants respectfully submit that the Examiner has not appropriately resolved the *Graham* factors, including the factors of determining the scope and content of the prior art and ascertaining the differences between the prior art and the claims that are at issue. Based on the following, Applicants maintain that the above-mentioned *Graham* factors actually work in favor of non-obviousness of the invention. Additionally, Applicants submit that since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides for combining the cited references is improper.

Applicants respectfully submit that the presently claimed invention is distinct from and unobvious over Leclef combined with Chen, for the following reasons.

Differences between the claimed invention and the prior art

The claimed invention relates to a method of producing coated fine particles in which core fine particles are coated with a lipid membrane. In the claimed invention, core fine particles are a complex of a drug and liposome. As recited in claim 1, the presently claimed invention requires within the steps that a liquid (liquid A) is prepared that contains a polar organic solvent selected from alcohols, glycols and polyalkylene glycols in which the core fine particles are dispersed and a lipid membrane component constituting the lipid membrane is dissolved. As discussed above, core fine particles are a complex of a drug and liposome.

In contrast, Leclef discloses a method of producing lipid microparticles. Specifically, the microparticles are those of a water-insoluble substance possessing an affinity for phospholipids and of at least one phospholipid (*See* Leclef, column 1, lines 14-16). As the Examiner pointed out, Leclef Example 1 discloses a microparticle of amphotericin B and Phosphatidylcholine (*See* Leclef, column 5, lines 44-55). However, Leclef also indicates that a new dosage form was developed based on the *interaction* of the medicinal product amphotericin B with Phosphatidylcholine to form a suspension of microparticles (*See* Leclef, column 5, lines 11-15). Applicants note that this is not the same as the core fine particles that are described above, which are then coated with a lipid membrane. Applicants contend that the above step in the presently claimed invention is neither taught nor disclosed in Leclef.

Further, Applicants also submit that the presently claimed invention requires that a liquid

(liquid B) be prepared that is miscible with liquid A and does not contain any polar organic solvent. The Applicants respectfully submit that the Examiner is incorrect when asserting the presently claimed invention's liquid B is described as the aqueous solution of Leclef's process. As indicated in Leclef, Leclef teaches that for polyene macrolide antimycotic medical products, the microparticles are prepared where the polyene macrolide antimycotic medical product and a phospholipid or phospholipids are dissolved in their common organic solvent in a basic or acid medium. A solution obtained is then mixed with an aqueous solution to obtain a precipitate, and then the solution is neutralized by adding acid or base, respectively (the neutralization can be carried out before or after addition of the aqueous solution; *See* Leclef, column 3, lines 31-65). Applicants reiterate that this is not the same as described in the presently claimed invention since Leclef makes it explicit that the polyene macrolide antimycotic medical product is not complexed with a liposome and then not subsequently coated with a lipid membrane. Applicants contend that the step of requiring that a liquid (liquid B) be prepared that is miscible with liquid A and does not contain any polar organic solvent is neither taught nor disclosed since Leclef does not teach or disclose the other requirements for the core fine particles or the required preparation of liquid A.

Concerning the next step of the claimed invention, liquid A is allowed to flow from at least one inlet of a device for producing coated fine particles equipped with an in-line mixing means having two or more inlets and one or more outlet(s) and letting liquid B flow from at least one remaining inlet to mix the liquids thereby coating the core fine particles with a lipid membrane.

As previously indicated, the Examiner admits that Leclef does not describe mixing the two solutions via a device equipped with a mixing means. Applicants again point out that not only does Leclef fail to describe the mixing of liquids A and B, it is also silent in disclosing the complex of a drug and liposome defined as the core fine particles. Applicants respectfully submit that the mixture of Leclef cannot be the lipid *coated* fine particles of the claimed invention.

Applicants respectfully submit that Leclef does not disclose any core fine particles that are a complex of a drug and liposome that are then coated with a lipid membrane, as well as not disclosing any method of coating the core fine particles with a lipid membrane.

With regards to the Chen reference, Chen only discloses a concurrent flow mixing method and apparatus for producing microparticles. As indicated above for the Leclef reference, the Chen microparticles are not the same as the coated fine particles of the present invention. The Examiner asserts that Chen discloses an apparatus that uses condensing agents such as liposomes, emulsions, microemulsions that produce the coated core fine particles of the present invention. Applicants respectfully disagree with this premise. In contrast, the present invention relates to a method of producing coated fine particles in which core fine particles, *i.e.*, a complex of a drug and liposome, are coated with a lipid membrane. Chen neither discloses coated fine particle as of the present invention, nor discloses any method for coating a core fine particles with a lipid membrane.

Since Leclef, in view of Chen, is silent to any complex of a drug and liposome as core fine particles and any method of coating the core fine particles with a lipid membrane, Applicants

respectfully submit that claims 1-4 and 10 are not obvious over Leclef in view of Chen.

In view of the above, it is submitted that the present invention as claimed is distinguished over the combination of Leclef and Chen. Further, Applicants also submit that Chen fails to compensate for, or teach, the deficiencies within Leclef. Therefore, the combinations of Leclef and Chen do not arrive at the present invention.

Applicants respectfully disagree with the Examiner that the present invention would be obvious to the skilled artisan. In view of the above, it is submitted that the present invention as claimed is distinguished over Leclef and Chen.

In light of the above remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the Leclef and Chen that would lead one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that these references are incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established.

Applicants respectfully request reconsideration and withdrawal of the present rejection, and Applicants submit that all of the rejections raised by the Examiner have been overcome, and that the present application now stands in condition for allowance.

CONCLUSION

Thus, Applicants respectfully request a timely Notice of Allowance for the present case.

In view of the above remarks, it is believed that claims 1-4 and 10 are allowable.

Should there be any outstanding matters that need to be resolved, the Examiner is respectfully requested to contact Paul D. Pyla at the telephone number below, in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized to charge payment or credit any overpayment to Deposit Account No. 23-0975 for any additional fees required under 37.C.F.R. §§1.16 or 1.17.

Respectfully submitted,

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